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## Ten common genetic variants associated with colorectal cancer risk are not associated with survival after diagnosis

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### Abstract

**Purpose**—To date, genome-wide association studies have identified ten genetic loci associated with colorectal cancer (CRC) susceptibility. We hypothesised that these loci might also impact on cancer survival.

**Experimental design**—To determine whether SNPs tagging these ten loci influenced all-cause and CRC-specific mortality, we prospectively followed survival outcomes for 2838 Scottish patients recruited soon after a diagnosis of colorectal cancer. Survival analysis was conducted using Cox proportional hazard models adjusted for American Joint Committee on Cancer stage, age and sex.

**Results**—None of the SNPs were found to be statistically significantly associated with all-cause or CRC-specific mortality.

**Conclusions**—We conclude that none of the ten common genetic variants so far shown to be associated with colorectal cancer risk are associated with survival from colorectal cancer.

### Keywords

Colorectal cancer; common genetic variants; all cause survival; colorectal cancer survival

## INTRODUCTION

Despite modest improvements in survival rates from colorectal cancer (CRC) over the last 25 years, deaths from CRC still account for approximately 10% of all cancer deaths in the UK. Globally, CRC is ranked second as a cause of cancer mortality with 492,000 deaths per

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annum (Cancer Research UK, 2007). The main CRC prognostic marker at present is stage at diagnosis, which describes tumour spread through the bowel wall, number of affected lymph nodes and spread of tumour to distant organs (metastasis) (1). Some studies have reported that lifestyle factors such as physical activity and body mass index influence particular characteristics of the tumour systemic inflammatory response, which affects cancer survival (2;3). We hypothesised that common genetic variation might also influence cancer survival. There is some evidence of familial concordance for survival in a number of cancers, including CRC, which suggests that inherited genetic variation can contribute to CRC prognosis (4). A few studies have reported associations with survival of genetic variants alone (5) or in combination with particular treatments (6;7). A study that investigated the association between survival and common genetic variants and haplotypes of the mismatch repair genes concluded that there is some evidence these variants may influence survival in CRC patients (1). Finally, a recent study found no associations between SNPs located on 8q24 and colon cancer survival in 460 stage 2 and 3 colon cancer patients (8).

Recently, Genome Wide Association Studies (GWAS) have demonstrated that part of the heritable component to risk of colorectal cancer (9) is attributable to common variants of individually modest effect. The risk loci so far identified map to 8q24 (rs6983267) (10;11), 8q23.3 (rs16892766, *EIF3H*) (12), 10p14 (rs10795668) (12), 11q23 (rs3802842) (13), 15q13 (rs4779584) (14), 18q21 (rs4939827, *SMAD7*) (13;15), 14q22.2 (rs4444235, *BMP4*) (16), 16q22.1 (rs9929218, *CDHI*) (16), 19q13.1 (rs10411210, *RHPN2*) (16) and 20p12.3 (rs961253) (16). This study examines a large prospectively-collected population-based cohort of CRC patients in Scotland and is the first report to our knowledge that examines whether these loci are also associated with all-cause or CRC-specific mortality.

## METHODS

### Description of study patient population

All CRC patients were of Scottish ancestry (defined as parents and all grandparents residing in Scotland) from a population-based case-control study of CRC (Study of Colorectal Cancer in Scotland, SOCCS; 1999-2006) (17). The work is subject to ethical approvals from the MultiCentre Research Ethics committee for Scotland, 18 Local Research Ethics committees, 18 Caldicott guardians and 16 NHS Trust management committees, and all participants provided written informed consent.

Patients were recruited as soon as possible after a confirmed diagnosis of adenocarcinoma of large bowel epithelium, in order to minimise survival bias. We recruited 52% of all CRC cases arising in Scotland during the recruitment period and 98.4% of the recruited cases were finally included in the SOCCS study (3,417 CRC cases). A Genome Wide Association Study (GWAS) was conducted for colorectal cancer risk and this has been described in more detail elsewhere (9-13, 15). Dominant polyposis syndromes, HNPCC or bi-allelic MYH mutation carriers were excluded from the GWAS analysis and the subsequent survival analysis. Genetic data were available for 3,017 CRC cases. Cases were excluded from the survival analysis for the following reasons: not enough DNA for DNA amplification (43 cases); genotyping failure (1 case); previously unrecognised carriers of another susceptibility allele (5 cases); gender discrepancies between our records and genotype (10 cases); date of diagnosis a year prior to study's initiation date (6 cases); missing data (AJCC stage: 98 cases; date of diagnosis: 14 cases); duplicates (2 cases). Therefore, 2838 cases were included in the survival analysis.

## Genotyping, quality control, variant selection

Three aliquots of 10ml of blood were collected from each case in one ACD and two sodium EDTA tubes. DNA was extracted from one of the EDTA tubes using Nucleon kits. Median DNA yield on samples was 327 $\mu$ g (range: 50-1197 $\mu$ g). Quality control procedures included spectrophotometric readings of every sample (either A260/280 or PicoGreen™), agarose gel electrophoresis of uncut and restriction enzyme cut DNA from 2% of samples and a control PCR on 1% of samples (13).

The variants were genotyped using a custom made Illumina array. Details of these methods together with information on quality control procedures have been described previously (13). Briefly, in Phase 1 1012 cases (aged  $\geq$  56 years old) were genotyped using Illumina HumanHap300 and HumanHap240S arrays on the Infinium platform. In phase 2, 2037 cases (aged <80 years old) were genotyped using the Illumina iSelect custom panel for the top ranked 15,008 SNPs that were most strongly associated with CRC risk. In both Phase 1 and 2, samples were distributed randomly and blinded to survival status within 96-well sample plates to minimize systematic genotyping bias due to batch-to-batch variations. Genotype call rates were high for both the HumanHap300 (99.92%) and HumanHap240S (99.85%) arrays. (13). The variants that were included in the current report were SNPs that had been found to influence CRC risk in recent GWAS (Supplementary table 1).

## Survival Analysis

The 2,838 cases that were included in the survival analysis were observed until death or 30<sup>th</sup> April 2008 (censored date), whichever came first. For 2,771 CRC cases (97.6%) date of diagnosis (incidence date) was provided by the Scottish Cancer Registry (SCR). All incidence dates were cross-checked with date of first pathology record and date of definitive clinical diagnosis which was taken as start of treatment (operation, radiotherapy or decision for palliative therapy). In 67 cases (2.4%), only incidence date extracted first pathology report collected at recruitment was available. Death certificates were provided by the General Register Office (GRO) for Scotland. There were 947 deaths from the start of recruitment to the censored date. The cause of death was determined by a physician examining all death certificates and there were 811 deaths that were due to CRC (86% of all deaths). The protocol devised for deciding whether the death was related to colorectal cancer is available upon request. In all cases, assignment of cause of death was blinded to the genotype of the deceased subject. Participant records were linked to SCR and to General Register Office (GRO) through the Community Health Index (CHI), which is a NHS population-based register of all individuals who are registered with a general practitioner (GP) in Scotland (95% completeness) (18).

To determine the cancer stage according to the American Joint Committee on Cancer (AJCC) system the following procedure was followed. For patients from the South East Scotland (SCAN region) computerised tomography (CT) scans were requested and individually checked for evidence of metastasis. For patients from the West and North of Scotland (WoSCAN and NoSCAN regions, respectively) the consultants of individual patients were contacted by letter requesting staging information and clarification of metastasis status for their patients. For the remaining cases individual general practitioners were contacted by letter. The stage distribution for SCAN, WoSCAN and NoSCAN was not statistically significant different (chi square test p-value 0.17). In addition, there was no significant difference in survival time between the different Scotland regions (mean range 4.2-5.2 years, median range: 4.3-6.3 years).

Survival analysis was performed using the G12BAF routine of the NAG library (FORTRAN) and the statistical package Intercooled STATA version 10.0 (Stata Corp,

College Station, Texas). The t-test was used to test differences in mean age and the Pearson  $\chi^2$  test was used to test differences in terms of sex and AJCC stage between deceased and survived/ censored cases. Cox proportional hazards models were used to calculate hazards ratios (HRs) between the SNPs and death adjusted for other risk factors: Model I (adjusted for AJCC stage, age and sex), Model II (adjusted for age and sex) and Model III (crude model). In the first analysis, death from any cause was the end point, whereas in the second analysis death from CRC was the end point with deaths from other causes being treated as censored. In addition, we ran the all-cause and CRC-specific survival analysis after AJCC stage stratification. The proportional hazards assumption was checked by fitting a model including time-dependent covariates on the exposures and testing if the time-dependent covariates are significant.

## RESULTS

Table 1 presents summary statistics by mortality group of factors influencing survival. AJCC stage was strongly associated with all-cause and CRC-specific mortality (chi-square p-value:  $<5 \times 10^{-7}$ ) and age was associated with CRC-specific mortality (t-test p-value 0.02; Table 1). General information about the survival analysis, including the numbers of persons at risk (at selected time points), numbers of events at selected time-points and follow-up information, is presented in Supplementary table 2.

We tested for an association between stage at presentation and genotype at each of the 10 SNPs (Supplementary table 3). We found a marginally significant effect for rs9929218 (chi-square test p-value: 0.02), with an over-representation of stage 1 and 2 cases and an under-representation of stage 3 and 4 cases for the GG genotype when compared to the AA and AG genotypes. However, this is neither significant when testing by individual stage nor in grouped stage categories when adjusted for multiple testing. Genotypes at all other SNPs showed no relationship with stage at representation (Supplementary table 3). The association between each SNP and tumour location (colon vs. rectal cancer) was tested and reported in Supplementary Table 4. We found a significant effect for rs4779584, rs4939827 and rs10411210 (chi-square test p-value: 0.001, 0.002 and 0.01 respectively).

In the multiple logistic regression analysis adjusted for AJCC stage, age and sex (Model I) none of the ten SNPs were associated with all-cause (Table 2) or CRC-specific mortality (Table 3). Applying models adjusted only for age and gender (Model II) and the crude model (Model III), the findings were similar for all-cause mortality (Table 2) and CRC-specific mortality (Table 3). However, the A allele of the rs16892766 SNP was associated with increased CRC-specific mortality in models II and III (p-value 0.04).

Next, we fitted a model including a time-dependent form of the covariates (AJCC, sex, and age) to check the proportional hazards assumption. The assumption was true for the SNP, age and sex covariates, but not for the AJCC stage covariate. We therefore re-run Model II stratified by stage (AJCC stage 1, 2 and AJCC stage 3, 4). The results are presented in Supplementary tables 5 (all cause mortality) and 6 (CRC-specific mortality). The T allele of the rs4939827 SNP was associated with an increased all cause mortality only for AJCC stage 1 and 2 (p-value 0.05) (Supplementary table 5). In addition, the G allele of the rs10411210 was associated with an increased CRC-specific mortality only for AJCC stage 1 or 2 cases (p-value 0.02) (Supplementary table 6). Finally, all-cause and CRC-specific analysis was conducted separately for colon and rectal cancer cases and there were no statistically significant effects of genotype on either colon or rectal cancer survival (Supplementary tables 7 and 8).

## DISCUSSION

### Main findings

GWAS for CRC have so far identified 10 loci that contribute to the heritable component of CRC risk. These genetic variants are common in populations of European ancestry and their identification has provided new insights into the aetiology of CRC (19). We hypothesised that these 10 loci might be also associated with survival to CRC. However, no association was found between any of the 10 SNPs previously reported to be associated with CRC risk and all-cause or CRC-specific mortality. When we stratified by AJCC stage (AJCC 1, 2 and AJCC 3, 4), only rs10411210 was found to be marginally associated with CRC-specific mortality in AJCC stage 1, 2 cases. However, due to the large number of hypotheses tested, we consider this to represent a false positive due to multiple testing.

### Strengths and limitations

The strengths of this study include the systematic and prospective nature of the collected dataset of CRC cases from almost all hospitals in Scotland. Cases were recruited as soon as possible after diagnosis in order to limit survival bias amongst those recruited and maximise the person-years of follow up. We therefore consider that this systematic study of cancer experience from across a whole country provides results that are broadly representative of the general population. In addition, data relevant to the survival analysis were of high quality since they were obtained from the Scottish registries GRO and SCR (which are known to have high levels of data quality and data completeness) after linkage of our participants with their databases using the CHI number. In addition, extra care was taken in order to determine the AJCC stage by experienced study clinicians reviewing individual CT scans and staging and metastasis information for every case.

Limitations of our study include the possibility of a relative under-representation of cases that were very ill at presentation and died very soon afterwards, even within the same hospital admission. It is therefore possible that the external validity of results may be limited for CRC patients of advanced AJCC stage or those who present with a complication such as bowel obstruction or perforation, or those who have additional co-morbidity that might have influenced their ability to survive, independent of cancer stage at presentation. It is very unlikely that treatment differences between hospitals could have affected survival because CRC clinical management is standardised in Scotland through the Scottish Intercollegiate Guidelines Network (\*\*SIGN). The objective of SIGN is to improve the quality of health care for patients in Scotland by reducing variation in practice and outcome.

### Conclusion

In conclusion, none of the 10 genetic loci so far reported to be associated with CRC risk are associated with either all-cause or CRC-specific mortality after diagnosis.

#### STATEMENT OF TRANSLATIONAL RELEVANCE

We have addressed a key aspect of translational cancer medicine, namely whether germline variation associated with cancer risk is associated with cancer survival. Germline determinants of outcome have enormous translational potential because genotyping could be used for prognostic value and also to inform clinical use of adjuvant therapies. The common germline genetic variants that we studied are very strong candidates as prognostic factors because each is associated with cancer risk and several tag biologically plausible genes. Through this robust analysis of a large prospective

\*\*SIGN Guidance is lodged at <http://www.sign.ac.uk/>



cohort of colorectal cancer cases, we report an important negative finding. The work is important both because it is comprehensive and also because it sets a benchmark to help minimise false positive reporting from future smaller studies. The work will also inform design of further studies of germline determinants of colorectal cancer outcome.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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**Table 1**

Summary statistics by mortality group of factors influencing survival

<i>All cause mortality</i>	<i>All cases</i> <sup>*</sup>	<i>Deceased cases</i>	<i>Survived/ censored cases</i>	<i>p-value</i> <sup>†</sup>
<b>Phase 1 &amp; 2</b>	<b>n=2838</b>	<b>n=947</b>	<b>n=1891</b>	
<i>Age (years)</i>	61.03 (11.22)	61.48 (11.75)	60.80 (10.94)	0.12
<i>Sex</i>				
Men	1630 (57.43%)	565 (59.66%)	1065 (56.32%)	
Women	1208 (42.57%)	382 (40.34%)	826 (43.68%)	0.09
<i>AJCC stage</i>				
1	541 (19.06%)	58 (6.12%)	483 (25.54%)	
2	977 (34.43%)	193 (20.38%)	784 (41.46%)	
3	891 (31.40%)	317 (33.47%)	574 (30.35%)	
4	429 (15.12%)	379 (40.02%)	50 (2.64%)	<5×10 <sup>-7</sup>
<i>CRC-specific mortality</i>	<i>All cases</i> <sup>‡</sup>	<i>Deceased cases</i>	<i>Survived/ censored cases</i>	<i>p-value</i>
<b>Phase 1 &amp; 2</b>	<b>n=2838</b>	<b>n=811</b>	<b>n=2027</b>	
<i>Age (years)</i>	61.03 (11.22)	60.24 (11.67)	61.34 (11.02)	0.02
<i>Sex</i>				
Men	1630 (57.43%)	471 (58.08%)	1159 (57.18%)	
Women	1208 (42.57%)	340 (41.92%)	868 (42.82%)	0.66
<i>AJCC stage</i>				
1	541 (19.06%)	27 (3.33%)	514 (25.36%)	
2	977 (34.43%)	132 (16.28%)	845 (41.69%)	
3	891 (31.40%)	280 (34.53%)	611 (30.14%)	
4	429 (15.12%)	372 (45.87%)	57 (2.81%)	<5×10 <sup>-7</sup>

\* Mean values and in parentheses standard deviations for quantitative variables; number of subjects and in parenthesis percentages for categorical variables.

<sup>†</sup> P-values from the Pearson  $\chi^2$  for categorical variables; from t-test for continuous variables

<sup>‡</sup> Mean values and in parentheses standard deviations for quantitative variables; number of subjects and in parenthesis percentages for categorical variables.

**Table 2**  
Association between the 10 SNPs reported to show statistically significant association with CRC risk and all cause mortality

SNP	Chromosome	Map	Ref allele	Ref allele freq	N	Model I*			Model II†			Model III‡		
						HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
rs6983267	8	128482487	T	0.44	2838	1.03	0.94, 1.13	0.57	0.97	0.88, 1.06	0.46	0.96	0.88, 1.06	0.44
rs16892766	8	117699864	A	0.90	2837	1.03	0.89, 1.19	0.71	1.12	0.97, 1.30	0.12	1.12	0.97, 1.29	0.13
rs10795668	10	8741225	A	0.32	2834	0.98	0.90, 1.08	0.74	1.02	0.93, 1.12	0.67	1.02	0.93, 1.12	0.71
rs3802842	11	110676919	A	0.65	2838	0.93	0.85, 1.02	0.14	0.98	0.90, 1.08	0.7	0.98	0.89, 1.08	0.68
rs4779584	15	30782048	T	0.21	2797	0.95	0.85, 1.06	0.36	1.00	0.89, 1.11	0.93	1.00	0.89, 1.11	0.96
rs4939827	18	44707461	T	0.56	2838	1.05	0.96, 1.15	0.33	1.09	1.00, 1.20	0.07	1.09	0.99, 1.20	0.07
rs4444235	14	53480669	T	0.52	2838	1.03	0.94, 1.13	0.53	1.02	0.93, 1.12	0.7	1.02	0.93, 1.12	0.69
rs9929218	16	67378447	A	0.26	2838	0.94	0.85, 1.04	0.26	0.91	0.83, 1.01	0.08	0.91	0.83, 1.01	0.08
rs10411210	19	38224140	T	0.07	2837	0.98	0.82, 1.16	0.79	1.04	0.87, 1.24	0.69	1.04	0.87, 1.24	0.68
rs961253	20	6352281	A	0.39	2837	1.07	0.97, 1.17	0.16	1.01	0.92, 1.11	0.79	1.02	0.93, 1.11	0.75

\* Adjusted for AJCC, age and sex

† Adjusted for: Age, sex

‡ Crude model

**Table 3**  
Association between the 10 SNPs reported to show statistically significant association with CRC risk and CRC-specific mortality

SNP	Chromosome	Map	Ref allele	Ref allele freq	N	Model I*			Model II†			Model III‡		
						HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
rs6983267	8	128482487	T	0.44	2838	1.06	0.96, 1.18	0.24	0.98	0.89, 1.08	0.68	0.98	0.89, 1.09	0.75
rs16892766	8	117699864	A	0.90	2837	1.06	0.91, 1.24	0.46	1.17	1.00, 1.37	0.04	1.17	1.01, 1.37	0.04
rs10795668	10	8741225	A	0.32	2834	0.99	0.89, 1.09	0.79	1.03	0.93, 1.15	0.54	1.04	0.94, 1.15	0.48
rs3802842	11	110676919	A	0.65	2838	0.95	0.86, 1.05	0.3	1.01	0.92, 1.12	0.83	1.01	0.92, 1.12	0.8
rs4779584	15	30782048	T	0.21	2797	0.94	0.83, 1.06	0.29	0.99	0.88, 1.21	0.92	0.99	0.88, 1.12	0.88
rs4939827	18	44707461	T	0.56	2838	1.05	0.95, 1.15	0.39	1.1	0.99, 1.21	0.07	1.1	0.99, 1.21	0.07
rs4444235	14	53480669	T	0.52	2838	1.02	0.93, 1.13	0.67	1.01	0.91, 1.11	0.86	1.01	0.92, 1.12	0.82
rs9929218	16	67378447	A	0.26	2838	0.94	0.84, 1.05	0.29	0.91	0.82, 1.02	0.1	0.91	0.82, 1.02	0.1
rs10411210	19	38224140	T	0.07	2837	0.99	0.82, 1.21	0.94	1.08	0.89, 1.31	0.46	1.08	0.89, 1.31	0.43
rs961253	20	6352281	A	0.39	2837	1.1	0.99, 1.21	0.07	1.03	0.93, 1.14	0.58	1.03	0.93, 1.14	0.57

\* Adjusted for AJCC, age and sex

† Adjusted for: Age, sex

‡ Crude model